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(54) Title: MACROLIDES			
(57) Abstract			
The invention relates to the stabilization of poly-ene macrolides and to a particular macrolide obtained in crystalline form.			

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MACROLIDES

The present invention relates to the stabilization of a pharmaceutically active ingredient sensitive to oxidation, e.g. a poly-ene macrolide, preferably a poly-ene macrolide having immunosuppressant properties, particularly rapamycins.

The handling and storage particularly in the bulk form of pharmaceutically active ingredients which are sensitive to oxidation is difficult. Special handling is necessary and often the oxidation-sensitive ingredient is stored in air-tight packaging under protective gas. Substantial amounts of stabilizers are added during the formulating process of such pharmaceutically active ingredients.

Poly-ene macrolides have satisfactory stability properties. However, it has now been found that their stability to oxygen may substantially be improved by the addition of a stabilizer, e.g. an antioxidant, during their isolation step.

According to the invention, there is provided

1. A process for stabilizing a poly-ene macrolide comprising adding an antioxidant to the purified macrolide, preferably at the commencement of its isolation step.

This process is particularly useful for the production of a stabilized poly-ene macrolide in bulk. The amount of antioxidant may conveniently be up to 1%, more preferably from 0.01 to 0.5 % (based on the weight of the macrolide). Such a small amount is referred to hereinafter as a catalytic amount.

As alternatives to the above the present invention also provides:

2. A mixture, e.g. a bulk mixture, comprising a poly-ene macrolide and an anti-oxidant, preferably a catalytic amount thereof, preferably in solid form.

The mixture may be in particulate form e.g. crystallized or amorphous form. It may be in a sterile or substantially sterile condition, e.g. in a condition suitable for pharmaceutical use.

3. Use of a mixture as defined above in 2. in the manufacture of a pharmaceutical composition.

Examples of poly-enes macrolides are e.g. molecules comprising double bonds, preferably conjugated double bonds, for example such having antibiotic and/or immunosuppressant properties, e.g. macrolides comprising a lactam or lactone bond and their derivatives, e.g. compounds which have a biological activity qualitatively similar to that of the natural macrolide, e.g. chemically substituted macrolides. Suitable examples include e.g. rapamycins and ascomycins. A preferred poly-ene macrolide is a macrolide comprising at least 2 conjugated double bonds, e.g. 3 conjugated double bonds.

Rapamycin is a known lactam macrolide produceable, for example by Streptomyces hygroscopicus. The structure of rapamycin is given in Kessler, H. et al.; 1993; *Helv. Chim. Acta*, 76 : 117. Rapamycin has antibiotic and immunosuppressant properties. Derivatives of rapamycin are known, e.g. 16-O-substituted rapamycins, for example as disclosed in WO 94/02136 and WO 96/41807, 40-O-substituted rapamycins, for example as disclosed in WO 94/09010, WO 92/05179, WO 95/14023, 94/02136, WO 94/02385 and WO 96/13273, all of which being incorporated herein by reference. Preferred rapamycin derivatives are e.g. rapamycins wherein the hydroxy in position 40 of formula A illustrated at page 1 of WO 94/09010 is replaced by -OR wherein R is hydroxyalkyl, hydroxyalkoxyalkyl, acylaminoalkyl or aminoalkyl, e.g. 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, and 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin.

Ascomycins, of which FK-506 and ascomycin are the best known, form another class of lactam macrolides, many of which have potent immunosuppressive and anti-inflammatory activity. FK506 is a lactam macrolide produced by Streptomyces tsukubaensis. The structure of FK506 is given in the Appendix to the Merck Index, 11th ed. (1989) as item A5. Ascomycin is described e.g. in USP 3,244,592. Ascomycin, FK506, other naturally occurring macrolides having a similar biological activity and their derivatives, e.g. synthetic analogues and derivatives are termed collectively "Ascomycins". Examples of synthetic analogues or derivatives are e.g. halogenated ascomycins, e.g. 33-epi-chloro-33-desoxy-ascomycin such as disclosed in EP-A-427,680, tetrahydropyran derivatives, e.g. as disclosed in EP-A-626,385.

Particularly preferred macrolides are rapamycin and 40-O-(2-hydroxy)ethyl-rapamycin.

Preferred antioxidants are for example 2,6-di-tert.-butyl-4-methylphenol (hereinafter BHT), vitamin E or C, BHT being particularly preferred.

A particularly preferred mixture of the invention is a mixture of rapamycin or 40-O-(2-hydroxy)ethyl-rapamycin and 0.2% (based on the weight of the macrolide) of antioxidant, preferably BHT.

The antioxidant may be added to the poly-ene macrolide at the commencement of the isolation steps, preferably the final isolation step, more preferably just prior to the final precipitation step. The macrolide is preferably in a purified state. It may be dissolved in an inert solvent and the antioxidant is added to the resulting solution, followed by a precipitation step of the stabilized macrolide, e.g. in an amorphous form or in the form of crystals. Preferably the mixture of the invention is in amorphous form.

The resulting stabilized macrolide exhibits surprisingly an improved stability to oxidation and its handling and storage, e.g. in bulk form prior to its further processing for example into a galenic composition, become much easier. It is particularly interesting for macrolides in amorphous form.

The macrolide stabilized according to the invention may be used as such for the production of the desired galenic formulation. Such formulations may be prepared according to methods known in the art, comprising the addition of one or more pharmaceutically acceptable diluent or carrier, including the addition of further stabilizer if required.

Accordingly there is further provided:

4. A pharmaceutical composition comprising, as active ingredient, a stabilized mixture as disclosed above, together with one or more pharmaceutically acceptable diluent or carrier.

The composition of the invention may be adapted for oral, parenteral, topical (e.g. on the skin), ocular, nasal or inhalation (e.g. pulmonary) administration. A preferred

composition is one for oral administration, preferably a water-free composition when the active ingredient is a lactone macrolide.

The pharmaceutical compositions of the invention may comprise further excipients, e.g. a lubricant, a disintegrating agent, a surfactant, a carrier, a diluent, a flavor enhancer, etc. It may be in liquid form, e.g. solutions, suspensions or emulsions such as a microemulsions, e.g. as disclosed in USP 5,536,729, or in solid form, e.g. capsules, tablets, dragées, powders (including micronized or otherwise reduced particulates), solid dispersions, granulates, etc., e.g. as disclosed in WO 97/03654, the contents of which being incorporated herein by reference, or semi-solid forms such as ointments, gels, creams and pastes. They are preferably adapted to be in a form suitable for oral administration. Preferably they are in solid form. The pharmaceutical compositions of the invention may be prepared according to known methods, by mixing the macrolide stabilized according to the invention with the additional ingredients under stirring; the ingredients may be milled or ground and if desired compressed, e.g. into tablets.

This invention is particularly interesting for rapamycin compositions in liquid or solid form. A particularly preferred composition is a solid dispersion, e.g. comprising a stabilized rapamycin according to the invention and a carrier medium, e.g. a water-soluble polymer such as hydroxypropylmethylcellulose, e.g. as disclosed in WO 97/03654.

The compositions of the invention are useful for the indications as known for the macrolide they contain at e.g. known dosages. For example, when the macrolide has immunosuppressant properties, e.g. rapamycin or a rapamycin derivative, the composition may be useful e.g. in the treatment or prevention of organ or tissue acute or chronic allo- or xeno-transplant rejection, autoimmune diseases or inflammatory conditions, asthma, proliferative disorders, e.g. tumors, or hyperproliferative vascular disorders, preferably in the prevention or treatment of transplant rejection.

The amount of macrolide and of the composition to be administered depend on a number of factors, e.g. the active ingredient used, the conditions to be treated, the duration of the treatment etc. For e.g. rapamycin or 40-O-(2-hydroxy)ethyl-rapamycin, a suitable daily dosage form for oral administration comprise from 0.1 to 10 mg, to be administered once or in divided form.

In another aspect, this invention also provides 40-O-(2-hydroxy)ethyl-rapamycin in a crystalline form, particularly in a substantially pure form. Preferably the crystal form is characterized by the absence or substantial absence of any solvent component; it is in non-solvate form.

40-O-(2-hydroxy)ethyl-rapamycin in crystalline form belongs to the monoclinic system. The resulting crystals have a m.p. of 146°-147°C, especially 146.5°C. To assist identification of the new crystalline form, X-ray diffraction analysis data are provided. The conditions under which these data are obtained are as follows:

Temperature	293(2)K
Wavelength	1.54178 Å
Space group	P2 ₁
Unit cell dimensions	
a	14.378.(2) Å
b	11.244(1) Å
c	18.310(2) Å
β	108.58(1)°
Volume	2805.8(6) Å ³
Z	2
Density (calculated)	1.134 g/cm ³
Absorption coefficient	0.659 mm ⁻¹
F(000)	1040
Crystal size	0.59x0.11x0.03 mm
θ range for data collection	2.55 to 57.20°
Reflections collected	4182
Independent reflections	4037 [R(int) = 0.0341]
Intensity decay	32%
Refinement method	Full-matrix least-squares on F ²
Data/restraints/parameters	3134/1/613
Goodness-of-fit on F ²	1.055
Final R indices [I>2 sigma(I)]	R ₁ =0.0574, wR ₂ =0.1456
Largest diff. peak and hole	0.340 and -0.184 e/Å ³

40-O-(2-hydroxy)ethyl-rapamycin in crystalline form may be prepared by dissolving the amorphous compound in a solvent e.g. ethyl acetate and adding an aliphatic hydrocarbon C_nH_{2n+2} ($n=5, 6$ or 7). After addition of the hydrocarbon, the resulting mixture may be warmed e.g. at a temperature of 25 to 50°C , e.g. up to 30 - 35°C . Storing of the resulting mixture may conveniently take place at a low temperature, e.g. below 25°C , preferably from 0 to 25°C . The crystals are filtered and dried. Heptane is preferred as an aliphatic hydrocarbon. If desired, nucleation procedures may be commenced e.g. by sonication or seeding.

The present invention also provides a process for purifying 40-O-(2-hydroxy)ethyl-rapamycin comprising crystallizing 40-O-(2-hydroxy)ethyl-rapamycin from a crystal bearing medium, e.g. as disclosed above, and recovering the crystals thus obtained. The crystal bearing medium may include one or more components in addition to those recited above. A particularly suitable crystal bearing medium has been found to be one comprising ca. 2 parts ethyl acetate and ca. 5 parts aliphatic hydrocarbon, e.g. heptane.

40-O-(2-hydroxy)ethyl-rapamycin in crystalline form has been found to possess *in vitro* and *in vivo* immunosuppressive activity comparable to that of the amorphous form. In the localized GvHD, maximal inhibition (70-80%) of lymph node swelling is achieved with a dosage of 3 mg with 40-O-(2-hydroxy)ethyl-rapamycin in crystalline form.

40-O-(2-hydroxy)ethyl-rapamycin may be useful for the same indications as known for the amorphous compound, e.g. to prevent or treat acute and chronic allo- or xeno-transplant rejection, autoimmune diseases or inflammatory conditions, asthma, proliferative disorders, e.g. tumors, or hyperproliferative vascular disorders, e.g. as disclosed in WO 94/09010 or in WO 97/35575, the contents thereof being incorporated herein by reference. In general, satisfactory results are obtained on oral administration at dosages on the order of from 0.05 to 5 or up to 20 mg/kg/day, e.g. on the order of from 0.1 to 2 or up to 7.5 mg/kg/day administered once or, in divided doses 2 to 4x per day. Suitable daily dosages for patients are thus on the order of up to 10 mg., e.g. 0.1 to 10 mg.

40-O-(2-hydroxy)ethyl-rapamycin in crystalline form may be administered by any conventional route, e.g. orally, for example tablets or capsules, or nasally or pulmonary (by inhalation). It may be administered as the sole active ingredient or together with other

drugs, e.g. immunosuppressive and/or immunomodulatory and/or anti-inflammatory agents, e.g. as disclosed in WO 94/09010.

In accordance with the foregoing, the present invention also provides:

5. A method for preventing or treating acute or chronic allo- or xeno-transplant rejection, autoimmune diseases or inflammatory conditions, asthma, proliferative disorders, or hyperproliferative vascular disorders, in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount of 40-O-(2-hydroxy)ethyl-rapamycin in crystalline form;
6. 40-O-(2-hydroxy)ethyl-rapamycin in crystalline form for use as a pharmaceutical, e.g. in a method as disclosed above;
7. A pharmaceutical composition comprising 40-O-(2-hydroxy)ethyl-rapamycin in crystalline form together with a pharmaceutically acceptable diluent or carrier therefor;
8. A kit or package for use in immunosuppression or inflammation, including a pharmaceutical composition as disclosed above and a pharmaceutical composition comprising an immunosuppressant or immunomodulatory drug or an anti-inflammatory agent.

The following examples illustrate the invention without limiting it.

Example 1: Crystallisation

0.5 g amorphous 40-O-(2-hydroxy)ethyl-rapamycin is dissolved in 2.0 ml ethyl acetate at 40°C. 5.0 ml heptane is added and the solution becomes "milky". After warming to 30°C, the solution becomes clear again. Upon cooling to 0°C and with scratching an oil falls out of the solution. The test tube is closed and stored at 10°C overnight. The resulting white voluminous solid is then filtered and washed with 0.5 ml of a mixture of ethyl acetate/hexane (1:2.5) and the resulting crystals are dried at 40°C under 5 mbar for 16 hours. 40-O-(2-hydroxy)ethyl-rapamycin in crystalline form having a m.p. of 146.5°C is thus obtained.

Crystallisation at a larger scale may be performed as follows:

250 g amorphous 40-O-(2-hydroxy)ethyl-rapamycin is dissolved in 1.0 l ethyl acetate under argon with slow stirring. This solution is heated at 30°C and then during 45 minutes, 1.5 l heptane is added dropwise. 0.25 g of seed crystals prepared as disclosed above are added under the same conditions in portions. The mixture is further stirred at 30°C over a period of 2 hours and the crystallisation mixture is cooled to 25°C over 1 hour and then to 10°C for 30 minutes and filtered. The crystals are washed with 100 ml of a mixture ethyl acetate/hexane (2:3). Subsequent drying is performed at 50°C and ca 5 mbar. m.p. 146.5°C

IR in KBr: 3452, 2931, 1746, 1717, 1617, 1453, 1376, 1241, 1191, 1163, 1094, 1072, 1010, 985, 896 cm⁻¹

Single X-ray structure with coordinates are indicated in Figures 1 to 3 below.

Example 2: Production of stabilized 40-O-(2-hydroxy)ethyl-rapamycin

100g 40-O-(2-hydroxy)ethyl-rapamycin are dissolved in 600l abs. ethanol. After addition of 0.2g BHT, the resulting solution is added dropwise with stirring to 3.0 l water within 1 hour. The resulting suspension is stirred for an additional 30 minutes. Filtration with subsequent washing (3x200 ml water/ethanol at a v/v ratio of 5:1) results in a moist white product which is further dried under vacuum (1mbar) at 30°C for 48 hours. The resulting dried product contains 0.2% (w/w) BHT.

The resulting product shows improved stability on storage. The sum of by-products and degradation products in % after 1 week storage are as follows:

Compound	50°C in open flask
Ex. 2 (0.2% BHT)	1.49
Without BHT	>10

The procedure of above Example may be repeated but using, as active ingredient, rapamycin.

CLAIMS

1. A mixture comprising a poly-ene macrolide and an antioxidant.
2. A mixture according to claim 1, wherein the antioxidant is present in an amount of up to 1% based on the macrolide weight.
3. A mixture according to claim 1, wherein the antioxidant is present in an amount of 0.2% based on the macrolide weight.
4. A mixture according to claim 1, wherein the antioxidant is 2,6-di-tert.-butyl-4-methylphenol.
5. A mixture according to claim 1, wherein the poly-ene macrolide is rapamycin or 40-O-(2-hydroxy)ethyl-rapamycin.
6. A mixture according to claim 1, in solide form.
7. A pharmaceutical composition comprising, as active ingredient, a mixture according to claim 1 together with one or more pharmaceutically acceptable carrier or diluent.
8. A process for stabilizing a poly-ene macrolide comprising adding an antioxidant to the purified macrolide.
9. 40-O-(2-hydroxy)ethyl-rapamycin in crystalline form.
10. The compound according to claim 9, in crystalline non-solvate form.
11. The compound according to claim 9, having a crystal lattice
 $a = 14.37 \text{ \AA}$, $b = 11.24 \text{ \AA}$, $c = 18.31 \text{ \AA}$, the volume being 2805 \AA^3
12. A pharmaceutical composition comprising a compound according to claim 11 or 12, together with one or more pharmaceutically acceptable diluents or carriers therefor.
13. A process for purifying 40-O-(2-hydroxy)ethyl-rapamycin, comprising crystallizing 40-O-(2-hydroxy)ethyl-rapamycin from a crystal bearing medium and recovering the crystals thus obtained.

FIGURE 1/3

Atomic coordinates and equivalent isotropic displacement parameters (\AA^2)
 (U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor)

	x/a	y/b	z/c	U(eq)
C(1)	.9065(6)	.0121(9)	.5077(5)	.060(2)
O(1)	.9239(4)	-.0736(6)	.5482(4)	.076(2)
C(2)	.8041(5)	.0615(8)	.4625(4)	.060(2)
C(3)	.7847(7)	.1748(10)	.4984(6)	.087(3)
C(4)	.7627(7)	.1515(10)	.5725(7)	.098(3)
C(5)	.6795(7)	.0653(11)	.5610(6)	.094(3)
C(6)	.7005(6)	-.0496(9)	.5256(5)	.074(3)
N(7)	.7272(4)	-.0269(6)	.4567(4)	.059(2)
C(8)	.6781(5)	-.0693(7)	.3883(5)	.055(2)
O(8)	.6965(4)	-.0432(6)	.3287(3)	.074(2)
C(9)	.5940(6)	-.1566(8)	.3784(5)	.056(2)
O(9)	.6074(4)	-.2513(6)	.4074(4)	.084(2)
C(10)	.4962(5)	-.1136(8)	.3223(5)	.057(2)
O(10)	.5045(4)	-.1009(6)	.2486(3)	.075(2)
C(11)	.4079(6)	-.1951(8)	.3160(5)	.068(3)
C(11M)	.4107(7)	-.3114(9)	.2776(6)	.088(3)
C(12)	.3135(6)	-.1252(10)	.2738(6)	.088(3)
C(13)	.3099(6)	-.0061(10)	.3115(7)	.099(4)
C(14)	.4002(6)	.0651(9)	.3156(6)	.078(3)
O(14)	.4868(4)	-.0019(5)	.3559(3)	.065(2)
C(15)	.4070(6)	.01811(10)	.3592(6)	.082(3)
C(16)	.4953(7)	.2564(8)	.3624(6)	.079(3)
O(16)	.4841(5)	.3639(6)	.4015(4)	.095(2)
C(16M)	.5697(8)	.4308(10)	.4288(7)	.102(3)
C(17)	.5056(6)	.2802(9)	.2841(6)	.073(3)
C(17M)	.4268(7)	.3541(11)	.2307(6)	.103(4)
C(18)	.5806(7)	.2368(10)	.2680(6)	.079(3)
C(19)	.6018(7)	.2458(11)	.1964(6)	.092(3)
C(20)	.6768(8)	.1937(12)	.1809(6)	.097(3)
C(21)	.7032(8)	.2069(13)	.1094(7)	.111(4)
C(22)	.7771(8)	.1565(15)	.0948(7)	.121(5)
C(23)	.8086(8)	.1781(16)	.0240(6)	.128(5)
C(23M)	.7254(9)	.2152(23)	-.0474(7)	.184(9)
C(24)	.8912(8)	.2643(18)	.0406(6)	.140(6)
C(25)	.9826(9)	.2329(20)	.1069(6)	.141(6)
C(25M)	1.0348(12)	.1245(20)	.0884(8)	.178(8)
C(26)	1.0512(10)	.3412(22)	.1293(7)	.157(8)
O(26)	1.1132(8)	.3601(21)	.0998(7)	.281(11)
C(27)	1.0375(8)	.4278(16)	.1891(7)	.118(5)
O(27)	1.0877(7)	.5366(13)	.1901(7)	.185(5)
C(27M)	1.0445(17)	.6202(22)	.1382(13)	.256(13)
C(28)	1.0824(7)	.3750(11)	.2699(6)	.091(3)
O(28)	1.1827(4)	.3501(7)	.2818(4)	.108(2)

FIGURE 1/3 (Cont.)

Atomic coordinates and equivalent isotropic displacement parameters (\AA^2)
(cont.)

	x/a	y/b	z/c	U(eq)
C(29)	1.0329(7)	.2733(10)	.2922(5)	.073(3)
C(29M)	.9318(6)	.2995(10)	.2984(6)	.094(3)
C(30)	1.0764(7)	.1700(10)	.3100(5)	.077(3)
C(31)	1.0376(7)	.0581(10)	.3340(5)	.081(3)
C(31M)	1.0198(9)	-.0385(13)	.2723(7)	.124(4)
C(32)	1.1046(7)	.0210(10)	.4103(6)	.079(3)
O(32)	1.1436(7)	-.0747(9)	.4183(5)	.132(3)
C(33)	1.1271(6)	.1025(9)	.4776(5)	.071(3)
C(34)	1.0764(5)	.0601(8)	.5342(5)	.062(2)
O(34)	.9735(3)	.0853(5)	.4967(3)	.071(2)
C(35)	1.1115(5)	.1217(9)	.6132(5)	.064(2)
C(35M)	1.1060(7)	.2562(10)	.6069(6)	.092(3)
C(36)	1.2149(6)	.0757(9)	.6578(5)	.072(3)
C(37)	1.2650(6)	.1298(9)	.7370(5)	.074(3)
C(38)	1.2091(7)	.1198(14)	.7935(5)	.110(4)
C(39)	1.2680(9)	.1650(16)	.8735(6)	.128(5)
O(39)	1.2082(8)	.1584(20)	.9206(6)	.243(9)
C(39M)	1.2099(20)	.2512(47)	.9702(17)	.498(36)
C(40)	1.3640(9)	.0982(13)	.9048(6)	.0116(4)
O(40)	1.4177(7)	.1412(10)	.9790(5)	.151(4)
C(41)	1.4221(7)	.1138(13)	.8506(6)	.110(4)
C(42)	1.3653(6)	.0697(11)	.7702(5)	.096(3)
C(43)	1.4272(14)	.0621(20)	1.0408(9)	.171(7)
C(44)	1.5146(20)	-.0307(24)	1.0549(10)	.238(12)
O(45)	1.4956(12)	-.1215(13)	.9899(7)	.215(5)

FIGURE 2/3

Bond lengths (Å)

C(1)-O(1)	1.193(10)	C(24)-C(25)	1.52(2)
C(1)-O(34)	1.329(10)	C(25)-C(25M)	1.53(2)
C(1)-C(2)	1.545(11)	C(25)-C(26)	1.54(3)
C(2)-N(7)	1.465(10)	C(26)-O(26)	1.20(2)
C(2)-C(3)	1.500(13)	C(26)-C(27)	1.53(2)
C(3)-C(4)	1.511(14)	C(27)-O(27)	1.42(2)
C(4)-C(5)	1.502(13)	C(27)-C(28)	1.533(14)
C(5)-C(6)	1.518(14)	O(27)-C(27M)	1.34(2)
C(6)-N(7)	1.453(10)	C(28)-O(28)	1.415(10)
N(7)-C(8)	1.315(9)	C(28)-C(29)	1.471(14)
C(8)-O(8)	1.237(9)	C(29)-C(30)	1.311(13)
C(8)-C(9)	1.523(11)	C(29)-C(29M)	1.523(12)
C(9)-O(9)	1.178(9)	C(30)-C(31)	1.497(14)
C(9)-C(10)	1.532(11)	C(31)-C(32)	1.482(13)
C(10)-O(10)	1.398(9)	C(31)-C(31M)	1.53(2)
C(10)-O(14)	1.425(10)	C(32)-O(32)	1.201(11)
C(10)-C(11)	1.540(11)	C(32)-C(33)	1.487(13)
C(11)-C(11M)	1.491(13)	C(33)-C(34)	1.521(11)
C(11)-C(12)	1.546(12)	C(34)-O(34)	1.447(9)
C(12)-C(13)	1.51(2)	C(34)-C(35)	1.537(11)
C(13)-C(14)	1.506(13)	C(35)-C(35M)	1.517(13)
C(14)-O(14)	1.441(10)	C(35)-C(36)	1.540(11)
C(14)-C(15)	1.516(14)	C(36)-C(37)	1.525(12)
C(15)-C(16)	1.511(12)	C(37)-C(38)	1.503(11)
C(16)-O(16)	1.439(11)	C(37)-C(42)	1.532(12)
C(16)-C(17)	1.512(14)	C(38)-C(39)	1.526(14)
O(16)-C(16M)	1.392(11)	C(39)-O(39)	1.399(13)
C(17)-C(18)	1.301(12)	C(39)-C(40)	1.51(2)
C(17)-C(17M)	1.491(13)	O(39)-C(39M)	1.38(4)
C(18)-C(19)	1.441(14)	C(40)-O(40)	1.417(13)
C(19)-C(20)	1.333(14)	C(40)-C(41)	1.50(2)
C(20)-C(21)	1.48(2)	O(40)-C(43)	1.41(2)
C(21)-C(22)	1.30(2)	C(41)-C(42)	1.521(14)
C(22)-C(23)	1.52(2)	C(43)-C(44)	1.59(3)
C(23)-C(24)	1.49(2)	C(44)-O(45)	1.52(2)
C(23)-C(23M)	1.52(2)		

FIGURE 3/3

Bond angles (°)

O(1)-C(1)-O(34)	125.1(7)	C(23)-C(24)-C(25)	116(2)
O(1)-C(1)-C(2)	126.8(8)	C(24)-C(25)-C(25M)	111.7(14)
O(34)-C(1)-C(2)	108.0(8)	C(24)-C(25)-C(26)	110(2)
N(7)-C(2)-C(3)	111.5(6)	C(25M)-C(25)-C(26)	111.9(12)
N(7)-C(2)-C(1)	111.3(7)	O(26)-C(26)-C(27)	120(2)
C(3)-C(2)-C(1)	110.4(7)	O(26)-C(26)-C(25)	122(2)
C(2)-C(3)-C(4)	111.6(9)	C(27)-C(26)-C(25)	118.5(12)
C(5)-C(4)-C(3)	111.8(9)	O(27)-C(27)-C(26)	112.2(12)
C(4)-C(5)-C(6)	110.6(7)	O(27)-C(27)-C(28)	105.4(12)
N(7)-C(6)-C(5)	111.4(8)	C(26)-C(27)-C(28)	109.5(12)
C(8)-N(7)-C(6)	123.5(7)	C(27M)-O(27)-C(27)	118.5(14)
C(8)-N(7)-C(2)	118.6(7)	O(28)-C(28)-C(29)	111.3(9)
C(6)-N(7)-C(2)	117.3(6)	O(28)-C(28)-C(27)	108.7(8)
O(8)-C(8)-N(7)	123.6(7)	C(29)-C(28)-C(27)	118.4(10)
O(8)-C(8)-C(9)	115.6(7)	C(30)-C(29)-C(28)	121.5(9)
N(7)-C(8)-C(9)	120.8(8)	C(30)-C(29)-C(29M)	122.9(10)
O(9)-C(9)-C(8)	121.3(7)	C(28)-C(29)-C(29M)	115.4(9)
O(9)-C(9)-C(10)	124.8(8)	C(29)-C(30)-C(31)	128.7(9)
C(8)-C(9)-C(10)	113.6(7)	C(32)-C(31)-C(30)	108.8(8)
O(10)-C(10)-O(14)	112.1(7)	C(32)-C(31)-C(31M)	113.7(10)
O(10)-C(10)-C(9)	109.7(6)	C(30)-C(31)-C(31M)	111.8(8)
O(14)-C(10)-C(9)	100.5(6)	O(32)-C(32)-C(31)	120.3(11)
O(10)-C(10)-C(11)	108.1(6)	O(32)-C(32)-C(33)	118.8(10)
O(14)-C(10)-C(11)	111.6(6)	C(31)-C(32)-C(33)	120.8(9)
C(9)-C(10)-C(11)	114.9(7)	C(32)-C(33)-C(34)	110.2(8)
C(11M)-C(11)-C(10)	114.3(7)	O(34)-C(34)-C(33)	104.8(6)
C(11M)-C(11)-C(12)	111.2(8)	O(34)-C(34)-C(35)	109.8(6)
C(10)-C(11)-C(12)	107.9(7)	C(33)-C(34)-C(35)	114.5(7)
C(13)-C(12)-C(11)	111.9(8)	C(1)-O(34)-C(34)	119.2(7)
C(14)-C(13)-C(12)	109.9(9)	C(35M)-C(35)-C(34)	112.6(8)
O(14)-C(14)-C(13)	109.8(8)	C(35M)-C(35)-C(36)	113.2(8)
O(14)-C(14)-C(15)	106.2(7)	C(34)-C(35)-C(36)	108.6(7)
C(13)-C(14)-C(15)	113.2(8)	C(37)-C(36)-C(35)	116.9(8)
C(10)-O(14)-C(14)	115.1(6)	C(38)-C(37)-C(36)	115.6(7)
C(16)-C(15)-C(14)	114.5(7)	C(38)-C(37)-C(42)	109.6(8)
O(16)-C(16)-C(15)	105.4(7)	C(36)-C(37)-C(42)	107.5(8)
O(16)-C(16)-C(17)	112.5(8)	C(37)-C(38)-C(39)	112.5(8)
C(15)-C(16)-C(17)	113.4(8)	O(39)-C(39)-C(40)	113.9(13)
C(16M)-O(16)-C(16)	114.0(7)	O(39)-C(39)-C(38)	108.2(10)
C(18)-C(17)-C(17M)	124.9(9)	C(40)-C(39)-C(38)	111.0(11)
C(18)-C(17)-C(16)	119.2(9)	C(39)-O(39)-C(39M)	119(2)
C(17M)-C(17)-C(16)	115.9(8)	O(40)-C(40)-C(41)	110.3(10)
C(17)-C(18)-C(19)	127.7(10)	O(40)-C(40)-C(39)	110.2(12)
C(20)-C(19)-C(18)	125.6(11)	C(41)-C(40)-C(39)	108.9(10)
C(19)-C(20)-C(21)	126.6(11)	C(43)-O(40)-C(40)	115.9(12)
C(22)-C(21)-C(20)	126.3(12)	C(40)-C(41)-C(42)	111.2(9)
C(21)-C(22)-C(23)	126.0(13)	C(41)-C(42)-C(37)	112.8(9)
C(24)-C(23)-C(23M)	111(2)	O(40)-C(43)-C(44)	114(2)
C(24)-C(23)-C(22)	111.4(10)	O(45)-C(44)-C(43)	112.2(14)
C(23M)-C(23)-C(22)	114.2(10)		

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(54) Title: STABILIZATION OF MACROLIDES			
(57) Abstract			
The invention relates to the stabilization of poly-ene macrolides and to a particular macrolide obtained in crystalline form.			

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A. CLASSIFICATION OF SUBJECT MATTER

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 09010 A (SANDOZ AG ; SANDOZ AG (DE); SANDOZ LTD (CH); COTTENS SYLVAIN (CH);) 28 April 1994 (1994-04-28) page 21 - page 22; example 8 ---	9-13
X	WO 97 03654 A (SANDOZ LTD ; SANDOZ AG (DE); SANDOZ AG (AT); GUITARD PATRICE (FR);) 6 February 1997 (1997-02-06) cited in the application page 6, line 9 - line 12 page 9, line 21 - line 24 ---	1-9, 12
X	WO 98 04279 A (HAEBERLIN BARBARA ; SCHUURMAN HENDRIK J (CH); CIBA GEIGY AG (CH); M) 5 February 1998 (1998-02-05) page 10, line 15 - line 17 page 18; examples 4-9 ---	1, 4, 5, 7, 8
	--- -/--	



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Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 423 714 A (FUJISAWA PHARMACEUTICAL CO) 24 April 1991 (1991-04-24) page 9; example 1	1,2,7,8
X	EP 0 041 795 A (AYERST MCKENNA & HARRISON) 16 December 1981 (1981-12-16) page 9, line 14 - line 26	1,7,8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/09521

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9409010 A	28-04-1994	AT 173736 T	15-12-1998
		AU 676198 B	06-03-1997
		AU 4819293 A	09-05-1994
		CA 2145383 A	28-04-1994
		CZ 9500899 A	13-09-1995
		DE 69322282 D	07-01-1999
		DE 69322282 T	12-05-1999
		EP 0663916 A	26-07-1995
		EP 0867438 A	30-09-1998
		ES 2124793 T	16-02-1999
		FI 951678 A	07-04-1995
		HU 71232 A	28-11-1995
		JP 11240884 A	07-09-1999
		JP 8502266 T	12-03-1996
		NO 951312 A	08-06-1995
		NZ 256026 A	27-08-1996
		PL 308268 A	24-07-1995
		RO 114451 A	30-04-1999
		RU 2143434 C	27-12-1999
		SK 46595 A	09-08-1995
		US 5665772 A	09-09-1997
WO 9703654 A	06-02-1997	AU 706174 B	10-06-1999
		AU 6615296 A	18-02-1997
		BE 1009856 A	07-10-1997
		BR 9609537 A	23-02-1999
		CA 2225960 A	06-02-1997
		CN 1195289 A	07-10-1998
		CZ 9800091 A	15-04-1998
		EP 0839028 A	06-05-1998
		FR 2736550 A	17-01-1997
		HU 9900391 A	28-06-1999
		IT RM960501 A	12-01-1998
		JP 11509223 T	17-08-1999
		NO 980081 A	08-01-1998
		NZ 313633 A	28-05-1999
		PL 324502 A	25-05-1998
		SK 4498 A	06-05-1998
		US 6004973 A	21-12-1999
WO 9804279 A	05-02-1998	AU 4012497 A	20-02-1998
		CA 2261666 A	05-02-1998
		EP 0956034 A	17-11-1999
EP 0423714 A	24-04-1991	AT 107499 T	15-07-1994
		CA 2027608 A	17-04-1991
		DE 69010139 D	28-07-1994
		DE 69010139 T	13-10-1994
		DK 423714 T	25-07-1994
		JP 2925285 B	28-07-1999
		JP 3204807 A	06-09-1991
		KR 159766 B	01-12-1998
		US 5215995 A	01-06-1993
EP 0041795 A	16-12-1981	AT 11218 T	15-02-1985
		AU 543727 B	02-05-1985
		AU 7093181 A	10-12-1981
		CA 1177399 A	06-11-1984

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/09521

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0041795 A		DE 3168276 D	28-02-1985
		ES 502647 D	01-10-1982
		ES 8207426 A	16-12-1982
		IE 51295 B	26-11-1986
		JP 57014523 A	25-01-1982
		PH 16723 A	25-01-1984
<hr/>			